Poster#221

UNIVERSITY of HOUSTON COLLEGE OF PHARMACY

Assessment and Proposed Revision of Clinical Trial *Clostridioides difficile* Infection Clinical Response and Outcomes Definitions

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BACKGROUND

- Standardized definitions for clinical response to *C. difficile* infection (CDI) are lacking
- Diarrheal definitions have shifted from ≥6 unformed bowel movements [UBM]/36 hr to less stringent ≥3 UBMs/24 hr
- CDI cure has also transformed from clinical definition to a more stringent using same measure of ≤3 UBMs/day for 24-48 hours
- Initial clinical cure and sustained clinical response are often used in contemporary clinical trials but rely on unvalidated diarrhea metrics
- Shift towards more restrictive CDI cure definitions has unintended consequences for drug approval, patients enrolled in clinical trials, and drug innovation

OBJECTIVE

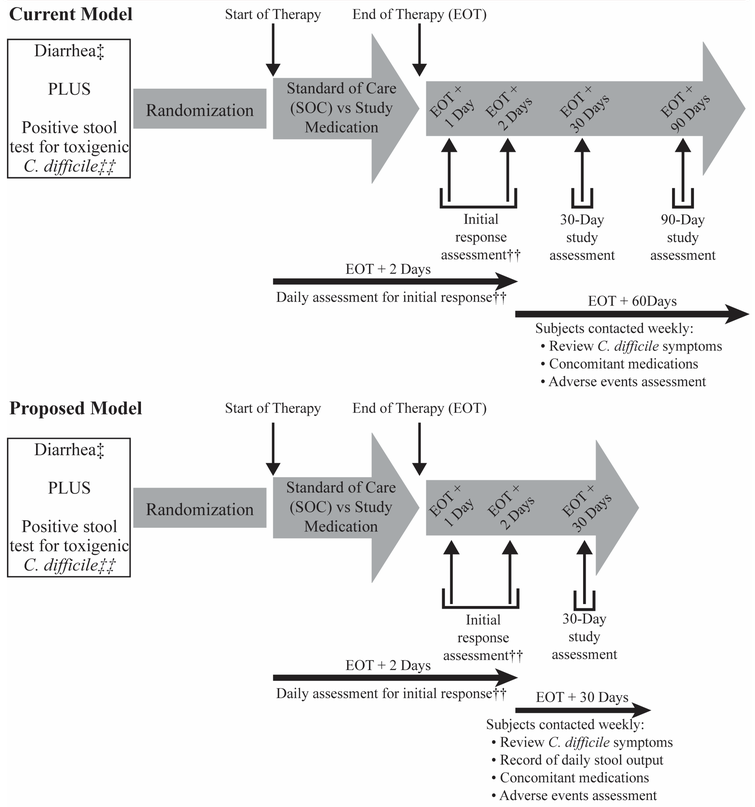
- **We created an international group of *C. difficile* experts to establish practical definitions that can be used from the bench to bedside for patients aged ≥2 years enrolled in *C. difficile* trials and for clinical management of patients with CDI.**

METHODS

- A multidisciplinary group of CDI experts met monthly from Jan.-Oct. 2022 to review response endpoints from published clinical trials of antibiotic therapy for CDI.
- Previously published phase III or IV trials of antibiotic therapy for CDI were included.
- Discussions were held to reach a consensus on new clinical trial endpoints for adults and children to improve the accuracy and clinical relevance of measures of treatment success.

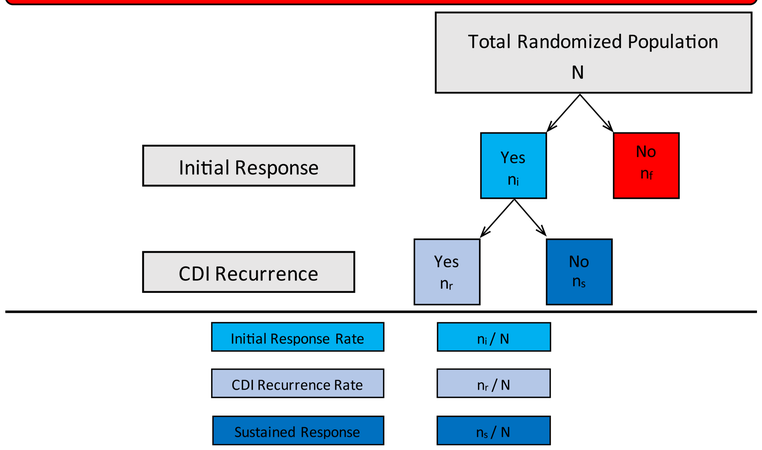
RESULTS

Figure 1. Timeline of CDI outcome assessments for clinical trials



‡ Diarrhea defined as 3 or more loose stools in 24 or fewer hours
‡‡ Diarrheal stool testing positive for toxigenic *C. difficile.* Specimen collected within 48 hours of randomization and before anti-CDI treatment
† Clinical cure defined as resolution of diarrhea (i.e., three or fewer stools for 2 consecutive days) AND maintenance of resolution requiring no further treatment for *C. difficile* infection within 2 days after the completion of therapy
†† Initial Response defined as any significant improvement in diarrhea (≤3 UBM/day, >50% reduction in UBM/day, , >75% decrease in stool volume for those with an ostomy, or attainment of bowel movements of Bristol Stool Form Scale types 1-4 on average) by day two after completion of CDI therapy

Figure 2. Patient flow for proposed CDI trial endpoints



Abbr.: N, total sample population; ni, population with initial response; nf, population with initial failure; nr, population with recurrence; ns, population with sustained response

Figure 3. Proposed outcome definitions for CDI clinical trials

Initial Response (IR)

- Any significant improvement in diarrhea by day two after completion of primary CDI therapy PLUS investigator determination that CDI treatmentcan be stopped
  - Improvement in diarrhea measured as any one or more of the following:
    - <3 unformed bowel movements/day
    - >50% reduction in number of stools
    - >75% decrease in stool volume (ostomy or rectal collection device)
    - Attainment of bowel movements of Bristol Stool Form Scale types 1-4 on average

Sustained Response (SR)

- Achievement of IR + no need for retreatment of CDI by day 30 after completion of primary CDI therapy

Table 1. Additional potential secondary study outcomes

Clinical	Microbiological
• Time to resolution of diarrhea (TTROD) • Time to recurrence (TTR) • Normalization of body temperature (if fever present during CDI episode) • Resolution of abdominal pain • Resolution of ileus (if present) • Resolution of megacolon (if present) • Improvement in baseline abnormal laboratory parameters such as elevated white blood cell count, elevated serum creatinine or decreased albumin, or improvement in inflammatory markers (such as C-reactive protein) • Resolution of pseudomembranes (if present) • Improvement in patient- or caregiver-reported symptoms such as flatulence, cramping, bloating, feeling tired, lack of energy, lightheadedness, dizziness, lack of appetite or nausea	• Normalization of primary to secondary bile acid ratio • Recovery of gut microbiota • Changes in minimum inhibitory concentration (MIC) of CDI drugs over the course of treatment

CONCLUSIONS

- **Initial Response (IR) and Sustained Response (SR) will more accurately capture success in treating CDI while highlighting the need for more research in this area.**
- As CDI management progresses to incorporate more non-antibiotic strategies, continued efforts are needed to ensure the accurate measurement of each treatment's effect either alone or in combination.

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